Abstracts from Invited Speakers

INFLAMMATORY AND NEUROPATHIC PAIN: NEW INSIGHTS INTO GENETIC DETERMINANTS

S.B. McMahon
King's College London, London, United Kingdom

Purpose: Pain sensitivity is known to vary considerably between people. This is true both for experimental pain, for instance where a standard force is applied to normal healthy tissue, but also for disease-related pain where osteoarthritis (OA) provides a particularly good example. It has long been recognised up to 50% of individuals with radiographic indications of OA disease do not report pain, and there is a poor correlation between pain and degree of radiographic change in OA. The influence of heritable (genetic) factors on pain sensitivity in general and OA pain in particular will be reviewed in this talk.
Methods: Results: Mutations in a few individual genes have recently been demonstrated to have a dramatic effect on pain appreciation. The best known example is mutations in the *trkA* gene, a number of which of lead to the development of congenital insensitivity to pain with anhydrosis (also know as hereditary sensory neuropathy type IV). These mutations lead to a failure of small diameter nociceptive neurones to develop. More recently mutations in a sodium channel gene normally expressed selectively in peripheral pain sensitive neurones (so-called Nav 1.7) have also been found to lead to both loss of function (congenital analgesia) and gain of function (erythromelagia) phenotypes.We have recently undertaken a classical twin study to evaluate the relative contributions of genetic and environmental factors on responses to painful stimuli in human volunteers to a wide variety of pain traits. Statistically significant genetic components (varying between 22-55%) were seen for the responses to the majority of painful stimuli including sensitivity to heating the skin, areas of secondary hyperalgesia brush evoked allodynia following a burn injury and iontophoresis of acid solutions.
Conclusions: Our study demonstrates the importance of genetic factors in determining human experimental pain sensitivity, and opens the way for its use as a phenotype in gene discovery. Since experimental pain sensitivity is known to be a predictor for pathological pain, our data imply that genetic factors have an important aetiological contribution towards clinical pain states.

ANIMAL MODELS FOR OA PAIN RESEARCH AND DRUG DISCOVERY

J.L. Henry
McMaster University, Hamilton, ON, Canada

Purpose: To address mechanisms underlying pain in an animal model of OA.
Methods: We have determined the effect of surgically-inducing derangement of one knee in the rat on properties of spinal and peripheral sensory neurons using single neuron electrophysiological recording.
Results: Mankin scoring of the joint in model rats over a five month period revealed progressive development of OA pathology. Articulation of the deranged knee in model but not sham-operated or naïve animals induced a brief hetero-segmental pro-nociceptive effect in the tail flick test. In a modified open field test model rats were less active than sham-operated or naïve rats, suggesting a decrease in voluntary use of the joint. Tests of mobilization on a slowly rotating drum confirmed that this decrease was not due to a reduction of the mechanical viability of the joint.
To assess the properties of spinal dorsal horn wide dynamic range (WDR) neurons, single neuron in vivo electrophysiology experiments were carried out. A significantly greater percentage of these neurons from model animals had spontaneous discharge rates $<$ 1 spike per sec. Furthermore only neurons from model animals exhibited an increase in discharge rate and a modulation of the pattern of spontaneous discharge following articulation of the knee. Articulation of the deranged knee also reduced the heterogeneity of the discharge patterns observed in response to touch and pinch stimuli. This decreased response range to non-noxious vs. noxious stimuli was accompanied by an articulation-induced increase in the number of low-threshold spike (LTS) bursts exhibited by neurons that responded to substance P. We propose that the pro-nociceptive effect of articulation is due in part to a change intrinsic to the WDR neurons that modulates sensitivity to innocuous and noxious stimuli.
In other experiments, intracellular recordings were taken from dorsal root ganglion neurons in vivo to identify changes that model induction would produce in the primary sensory neurons, in order to lead to a better understanding of the peripheral mechanism and also the initiation of the pain in osteoarthritis. Surprisingly, it was found that large myelinated neuron, both high threshold and low threshold neurones, underwent significant changes in our rat model of OA, and the changes observed differ from those identified by others in models of inflammatory pain.
Conclusions: These studies have led to the identification of unanticipated changes in both spinal cord and primary sensory neurons. They thus raise new avenues to explore to understand the pain of OA, as well as to develop novel therapeutic approaches to treat the pain of OA. It can also be concluded that a multidisciplinary approach, such as that used here, is appropriate to assess novel therapeutics that might modify the originating disease, the clinical manifestation of pain, or both.
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STRUCTURAL CORRELATES OF OA PAIN: MRI OF THE KNEE

P.R. Kornaat
Leiden University Medical Center, Leiden, The Netherlands

Although radiographs remain the usual means of assessing osteoarthritic changes in the knee, the association between osteoarthritic findings on radiographs and OA pain is poor. Fortunately, another imaging modality, magnetic resonance (MR) imaging, allows another perspective on the structural abnormalities associated with OA. MR imaging, with its excellent soft-tissue contrast, is the best non-invasive technique currently available for the assessment of cartilage injury and other internal dearrangements of the knee.
A major hallmark of OA is cartilage loss. The exact cause of knee pain in patients with OA remains enigmatic because hyaline cartilage does not contain pain fibres and as such cannot be the direct cause of pain in OA. Pain fibres are present in other structures in the knee including the joint capsule, the periosteum,